ABSTRACT
A NON-INVASIVE APPROACH FOR SEVERITY ASSESSMENT TO PREVENT REFRACTORY HYPERTENSION IN PATIENTS WITH AORTIC COARCTATION

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Coarctation of the aorta (CoA) is a constriction of the thoracic aorta and is one of the most common congenital cardiovascular defects. Guidelines for intervention include a transcatheter peak-to-peak pressure gradient ≥20 mmHg. Unfortunately, hypertension remains common despite successful CoA repair, and with prevalence increasing as a function of age at surgery. We hypothesize that adverse vascular persisting after CoA removal continue to deviate local hemodynamics from the preferred homeostatic state; hence, creating a positive feedback loop leading to refractory hypertension. Mechanistic investigation of this irreversible cycle of events is challenging among humans due to heterogeneity and a relatively small number of patients. Therefore, in the current work, a rabbit model was used with mechanically induced CoA to quantify hypertension precursors, including arterial thickening, stiffening, and vasoactive dysfunction. This allowed for investigating new intervention thresholds and potential translational approaches under experimentally controlled conditions. In the current proposal we aim to 1) identify kinetics of the stress-mediated aortic response to coarctation-induced mechanical stimuli for physiological determination of thresholds that prevent hypertension precursors post-treatment, 2) develop a Doppler-based severity assessment suitable for the transfer of identified thresholds to human CoA, and 3) identify the effect of concomitant morphological anomalies often co-existing with CoA. Results from aim 1 showed irreversible HTN precursors at peak-to-peak CoA gradients milder than 20 mmHg with kinetics correlated to the duration of CoA. Identified constitutive parameters for the established growth and remodeling mathematical model serve as a predictor for accurate identification of these severity and duration thresholds. Results from aim 2 showed that the newly derived non-invasive index of diastolic flow continuation and associated pressure gradient, i.e., continuous flow pressure gradient (CFPG), is a strong predictor of invasive CoA gradient measurements. As verified in groups of rabbit (n=34) and human (n=25) with CoAs, CFPG yielded improved diagnostic performance relative to conventional Doppler-derived indices. Aim 3 results showed that the proposed CFPG index is less sensitive to concomitant morphological anomalies often coexisting with CoA when compared to the conventional simplified Bernoulli equation. Collectively, the results from these aims provide computational tools for the identification of the well-needed severity and duration thresholds to prevent hypertension in CoA post-treatment; moreover, providing an echo-based assessment approach based on patient-specific factors for accurate transfer of these pre-clinical findings back to the clinics.